

EDITORIAL

The Human Alzheimer Disease Project

A New Call to Arms

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The message of this Editorial is simple and straightforward. For the past decade or more, billions of dollars have been invested by the pharmaceutical industry and the National Institutes of Health (NIH) to develop effective therapies for Alzheimer disease. Despite these vast sums of money, an effective therapy to delay or prevent Alzheimer disease has not been developed. Seeing the lack of progress, several major pharmaceutical companies have reduced or eliminated their Alzheimer disease efforts. The result means that without an effective therapy, the number of individuals in the United States who will develop Alzheimer disease in the next 25 years will increase from about 5.5 million to 12 million or more. In a recent analysis of the state of US health from 1990 to 2010, Murray and colleagues¹ reported that Alzheimer disease had increased more in rank (from 32 to 9) of years lost to life because of premature mortality compared with any other major disease during this 20-year period. On a worldwide basis, approximately 50 million persons will develop Alzheimer disease by 2050. Further, as we all know, it is not just the individual with Alzheimer disease who is affected but entire families, including spouses, children, and significant others who are mobilized to help the affected individual.

The biology of this disease is clearly formidable. The pathogenesis of Alzheimer disease involves a major segment of the human genome. It interacts with the aging process and other comorbidities, including cerebrovascular disease, hypertension, diabetes mellitus, and the metabolic syndrome. Loss of synapses and brain atrophy are consequences and these events are irreversible, making early intervention essential.

Currently, 3 monoclonal antibody therapies are being used in clinical trials of individuals who are cognitively asymptomatic but at risk for Alzheimer disease by virtue of accumulating β -amyloid as shown by positron emission tomography. It is the hope that very early intervention to block β -amyloid storage will prevent the secondary pathologies from beginning and progressing independently.²⁻⁵ The results of these clinical trials are eagerly awaited. The concern is that β -amyloid may not be the earliest pathology and that more antecedent neurodegenerative changes, such as the accumulation of tau, may already be in place and will function to render loss of synapses, induce atrophy, and more diffusely reduce glucose level uptake and metabolism. In addition, the interaction of various pathological processes is unknown.

Substantial progress has been made through the development of the Alzheimer Disease Centers Programs established by the National Institute on Aging (NIA). A network of 27 NIA-funded centers at medical schools across the country are highly

effective in developing research, clinical, and educational programs. Hundreds of first-rate research papers are published annually and are funded by the NIA through the Alzheimer Disease Centers Programs. Advances in understanding the etiology, differential diagnosis, and progression of Alzheimer disease and related disorders have clearly resulted. Great credit goes to Creighton H. Phelps, PhD, director of the Alzheimer Disease Centers Programs at the NIA, and his staff, including Nina Silverberg, PhD, who developed this network during the past 22 years. His remarkable efforts follow the pioneering efforts of Zaven Khachaturian, PhD, and Terry Radebaugh, PhD, who founded the program 30 years ago.

Federal investment in other major health issues has been successful. Support for cancer research through the National Cancer Institute is approximately \$5 billion per year. Support for heart disease research through the National Heart, Lung, and Blood Institute is approximately \$3 billion per year and human immunodeficiency virus/AIDS receives \$3 billion per year. Through the NIA and other institutes, the NIH is able to provide only about 10% of those levels of support by funding about \$600 million per year for Alzheimer disease research. The rates of several major cancers, heart disease, and stroke have decreased in recent years as a consequence of these appropriately generous levels of NIH support. What is now needed is equivalent support of Alzheimer disease and other related diseases, including frontotemporal degeneration and dementia with Lewy bodies.

A new emphasis is necessary to capture the urgency of the problem and to motivate the public and the US Congress to act decisively. Alzheimer disease is as horrific a disease as cancer, heart disease, and stroke. It deserves to be singled out and receive a level of attention and research dedication comparable to the other major causes of death and disability in the United States.

A focused exemplary research group dedicated to complex biological issues or diseases has precedence for achieving scientific success. The great clinical and scientific successes of the Neurological Institute of Columbia University Medical Center and the Montreal Neurological Institute of McGill University are examples where talent coming together for a specific set of neurological causes produced exponential growth in science. The members of The Laboratory of Biochemical Genetics at the NIH directed by Nobel Laureate Marshall Nirenberg in the 1960s deciphered the genetic code, the universality of the genetic code for all life forms. This research enterprise was concentrated, intense, and highly focused to achieve a single scientific purpose of deciphering the

genetic code. One of the authors (R.N.R.) was privileged to be a postdoctoral fellow in the laboratory and witnessed how a talented and committed group with incredible leadership produced phenomenal results.

The planning of the Medical Research Council of the United Kingdom in the 1960s to develop the new field of molecular biology with the creation of The Laboratory of Molecular Biology at Cambridge University became a national research priority and effort. Members included Hugh Huxley, John Kendrew, Francis Crick, Max Perutz, Fred Sanger, and Sidney Brenner, culminating in 6 Nobel Prizes, 2 of them given to Fred Sanger. This is a relevant example of how both funding and dedication to a single theme with concentrated leadership changed the world of science and brought therapies across the spectrum of genetic diseases. The analogy to Alzheimer disease is clear, as it is a genetic disease of enormous complexity requiring a dedicated singular focus and structure.

The sequencing of the human genome reported simultaneously in 2001 by an international consortium of genome sequencing centers in the United States led by Eric S. Lander of the Whitehead Institute for Biomedical Research, Francis Collins at the NIH, J. Craig Venter at Celera Genomics, and Jane Rogers and John Sulston at the Sanger Centre in England represents the finest example of a monumental collaborative and competitive scientific achievement.^{6,7} It provided, for the first time, deep genomic insights into the structure of the human genome and basic biological functions of living organisms, human genetic diseases, cancer, and human evolution. The consortium has already provided a road map for finding at-risk genes causal of Alzheimer disease. The \$3 billion needed to achieve the human genome sequence is more than justified by virtue of the therapies for many human diseases being developed as a result of data gleaned from it. An international consortium of a similar magnitude in talent and funding is now needed to decipher the cause of Alzheimer disease and deliver effective therapy.

In 1976, in the *Archives of Neurology* (our journal's former name), Robert Katzman⁸ called attention for the first time to Alzheimer disease as a major national health issue, pointing out how malignant the disease can be. It was a call to arms, citing the urgency to deal with Alzheimer disease. Today, 39 years later, we ask for a new call to arms, one even more urgent and more poignant based on the increasing epidemic.

Alzheimer disease is nonpartisan. It affects conservatives, liberals, Republicans, Democrats, rich individuals, poor individuals, and people of all races and ethnicities. Alzheimer disease affected President Reagan. Attention to this national medical tragedy requires a new level of commitment. Desperate diseases require desperate measures. Advancing the national medical research agenda for Alzheimer disease with full recognition of its effect on population health and the medical economics of the nation and coming to grips with its formidable complexity requires a rededication and creation of laboratories and centers focused at the highest scientific level to decipher the causation of Alzheimer disease and develop effective therapeutics.

In 2011, the US Congress passed the National Alzheimer Project Act signed by President Obama, establishing by law the

need "to accelerate the development of treatments that would prevent, halt, or reverse the course of Alzheimer's" by 2025.⁹ There is a national resolve to quicken the pace of Alzheimer disease research based on this legislation. However, it is a hollow victory because no new significant funding has accompanied the law. One of the recommendations of the Advisory Council on Research, Care, and Services for the National Alzheimer Project Act pertains to increasing the federal budget of Alzheimer research to \$2 billion.

There may be hope for a major brain equivalent to the Human Genome Project on the distant horizon, which could translate into Alzheimer disease research. On April 2, 2013, President Obama announced the Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative, which will be a partnership between the NIH, National Science Foundation, Defense Advanced Research Projects Agency, private foundations, and researchers. Cochairs of the BRAIN Initiative are Cornelia Bargmann, PhD, Rockefeller University, and William T. Newsome, PhD, Stanford University. An understanding of how the brain works is the overriding objective and the technologies that will be used relate to determining the human brain connectome, multielectrode arrays for recording from hundreds of neurons at once, optogenetics to target specific neurons for activation or inactivation with light, computational neuroscience to identify signals from neuronal populations, and gene expression profiles.¹⁰

In 2015, Francis Collins, NIH Director, states the BRAIN Initiative "will help to provide a foundational platform for major advances in Alzheimer disease" and other disorders.¹¹ Alzheimer disease research is not a primary research objective of the BRAIN Initiative but rather may achieve possible translational benefits down the road. So we remain concerned about seeing a concerted direct effort applied to Alzheimer disease research with the necessary funding support advocated here through the BRAIN Initiative. We believe the Human Alzheimer Disease Project as with the Human Genome Project better defines the necessary magnitude of effort, focus, and funding that will be required.

In 2013, Prime Minister David Cameron dedicated the last summit of his G8 presidency to dementia. This meeting and the subsequent legacy events have brought attention to the global nature of dementia and Alzheimer disease. He subsequently appointed a World Dementia Council to carry on the recommendations stemming from the 2013 summit. International momentum is building and the United States needs to be at the forefront. One suggestion from the G8 meeting implied that the member countries should consider investing 1% of their care costs for dementia into research. The United States spends more than \$200 billion per year caring for persons with dementia, which would translate into a \$2 billion research budget.¹²

The scope of the tragedy of Alzheimer disease presented by the Rand Corporation report in 2013 estimated the total monetary cost of dementia in 2010 was between \$159 billion and \$215 billion. Without a dramatic increase in the funding commitment by the US Congress of \$2 billion per annum for this new call to arms to achieve effective therapy, the costs will rise to more than \$511 billion by 2040.¹³

The time is now for the public, the US Congress, and the scientific community to achieve this highest level of scientific commitment to understand and treat this disease. The call to arms against Alzheimer disease is urgent and requires action.

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